UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,671	02/28/2002	Samuel Weiss	032901-039	2544

21839 7590 07/27/2004

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,671	WEISS ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-20-02, 3-13-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I, claims 1-8 and species of neurodegenerative diseases or conditions of a) brain injury, in the reply filed on 5-7-04 is acknowledged.

2. Claims 9-21are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 5-7-04.

Claim Rejections - 35 USC § 112

3. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification describes 2 methods of increasing neural stem cell number. Specifically, in Example 1, pregnancy in comparison to non-pregnant females is shown to increase neural stem cell number in association with female hormones elevated during pregnancy and in Example 3, addition of EGF and estradiol to Pass 1 neurospheres in culture is noted to increase neural stem cell numbers in comparison to culture with EGF alone. However, the claims as written include providing an effective amount of an estrogen to at least one neural stem cell under "conditions" which result in an increase in the number of

neural stem cells. While the specification discloses in vitro culture of neurospheres with EGF and pregnancy as suitable "conditions" to raise neural stem cell number, the artisan provides no guidance as to what other "conditions" are suitable to obatain increases in neural stem cell number. The two methods appear to bear little correlation and the pregnancy model fails to provide sufficient evidence that the increased neural stem cell numbers is the result of providing an estrogen. Further, the art appears to be unpredictable with respect to the provision of estrogen and the result of increasing neural stem cell number. In particular,

Thus, the instant disclosure of pregnancy and in vitro cell culture, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera of "conditions" that result in increased neural stem cell number via the provision of estrogen. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive

means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

Given the unpredictability of the art with respect to suitable conditions whereby estrogen mediates increased neural stem cell numbers, and the fact that the specification fails to provide objective evidence of any other "conditions" suitable to provide for the noted effects, it cannot be established that a representative number of species have been disclosed to support the genus claim in particular as encompassing numerous in vitro and/or in vivo preparations. There is no cause/effect correlation or nexus provided between the two model systems and any other in vitro or in vivo model system that evidences provision of estrogen is effective to increase neural stem cell number. Thus, for the aforementioned reasons, the specification lacks adequate written description supoort.

4. Claims 1-8 are rejected under 35 U.S.C. 112, flrst paragraph, because the specification, while being enabling for increasing neural stem cell number in vitro comprising providing an effective amount of an estrogen to at least one neural stem cell under conditions which result in an increase in the number of neural stem cells, does not reasonably provide enablement for practicing said method in vivo or in a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn broadly to methods of increasing neural stem cell numbers via administration of an estrogen under conditions which result in an

increase in the number of neural stem cells. The language of said claims encompasses both in vivo and in vitro uses in any animal via providing an estrogen.

The specification teaches that pregnant female mice show approximately 40% more neural stem cells than virgin mice in the subventricular zone (SVZ). Also, ovarectomized mice show a 36% redudion in neural stem cells in the subventricular zone (SVZ). Finally, neural stem cell cultures in vitro, incubated with a combination of EGF and estradiol show increased numbers of neural stem cell growth than with EGF alone (pp. 15-17). However, the specification fails to provide any other guidance for appropriate model systems or assays whereby in vitro or in vivo increases in neural stem cell number are achieved.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation because the artisan is unapprised of what other "conditions" are suitable conditions whereby contact with an estrogen mediates neural stem cell increases. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The specification does not enable the broad scope of the claims which encompasses a multitude of equivalent conditions because the specification does not teach which conditions can or should be modified such that increases in neural stem cell numbers are maintained. The relative skill of the art related to

the relationship between estrogens and neural stem cell proliferation is highly unpredictable.

In particular and with respect to Applicants in vivo model, Shingo et al., (3 January 2003) teach "Pregnancy-stimulated Neurogenesis in the Adult Female Forebrain Mediated by Prolactin." Science 299: 1 17-120. In particular, Shingo similarly notes that pregnant mice showed increased neurogenesis versus virgin mice (pp. 1 17). However, Shingo et al., sought to differentiate between the different hormones active in pregnancy that contribute to neurogenesis in the subventricular zone (SVZ) and olfactory bulb. Shingo et al., found in direct opposite to Applicants that, "whether infused directly into the brain or peripherally to normal or ovarlectomlzed females, estrogen and/or progesterone falied to increase the numbers of Brdu- immunoreactive cells in the SVZ (Table S1). Taken together, these data suggest that although circulating maternal hormones are likely responsible for the pregnancy- and pseudopregnancy-induced Increases In forebrain SVZ neurogenesis, estrogen and/or progesterone are not candldates for medlating this response," see in particular p. 117, column 3. Further, Shingo et al. demonstrated that prolactin is the most likely candidate for the neurogenesis seen in pregnant and pseudopregnant mice, see in part;icular p. 118-119, and Figures 1-3.

Moreover and with respect to Applicants in vitro model, Zhang et al., (IDS, 5-20-02) teach that cultured neurons from E14 cortex exhibit differentiation of neurons in response to contact with estrogen but that the neither estrogen or testosterone affected proliferation. Thus finding is also in direct opposite to

Applicants invention. In particular, Zhang teaches that estrogen is unable to provide for increased neural stem cells upon culture with estrogen. These cultures are similar as noted in Applicant's specification, see in particular p. 16, using E14 SVZ neurons. While Zhang is from cortex the cells are noted to exhibit proliferation and differentiation and thus the cells are neural stem cells as defined in Applicants specification. Hence there appears to be significant variability amongst neural stem cell response to estrogen. Yet the artisan fails to teach those critical elements that engender particular cells to respond to estrogen and hence predictability within neuronal stem cells and this type of model system is not established.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the animal" in reference to claim 1, for which there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Wade et al., J. of Neurosci., 19(16):6994-7006, Aug. 15, 1999 (5-20-02 IDS reference).

Wade et al., teach actions of estrogen on conditionally immortalized cerebral cortical neuroblasts, see in particular Title. The neuroblasts are deemed to be neural stem cells in that the cells are noted to be capable of proliferation (neurogenesis) and differentiation into either astrocyes, immature postmitotic neuroblasts, or to differentiate to neurons as stimulated via estrogen and neurotrophins, see in particular Abstract. Oligodendrocytic markers are also noted as in Table 1, p. 7001. Hence, the Wade cells are neural stem cells as described via Applicants specification and discussion of neural stem cells as having such properties, see specification pp. 7-8. The Wade reference teaches in particular at p. 6999, column 1-2, paragraph spanning that an estrogen in the form of estradiol-17β was capable of significantly increasing neuroblast

proliferation as measured via BrdU incorporation. The Wade cells are cultured in vitro. Thus, the reference teachings anticipate the claimed invention.

9. Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakafuku et al., J. of Neurosci. Res., 41:153-68, 1995 (3-13-03 IDS reference).

Nakafuku et al., teach a multipotential neural cell that that can conditionally generate neurons, astrocytes and oligodendrocytes in vitro, see in particular Title, Abstract. The MNS-57 cells are noted to proliferate upon contact with oestrogen and their growth is further stimulated when in combination with oestrogen and either bFGF or EGF, see in particular Abstract. The MNS-57 cells are deemed to be neural stem cells in that the cells are noted to be capable of proliferation and differentiation into either neurons, astrocyes, or oligodendrocytes as similarly described via Applicants specification and discussion of neural stem cells as having such properties, see specification pp. 7-8. The Nakafuku cells are cultured in vitro. Thus, the reference teachings anticipate the claimed invention.

10. Claims 1-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Tanapat et al., J. of Neurosci., 19(14):5792-5801, July 15, 1999 (5-20-02 IDS reference).

Tanapat et al., teach that estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat, see in particular Title, Abstract, Experiments 1-3, column 1, p. 5793, and p. 5797, column 2. Experiment 3 notes administration of an estrogen via injection with 17-

β-estradiol as in claim 8. Experiment 2 notes provision of an estrogen in females particularly during proestrus, the time of maximal estrogen production. The increased cells are noted to be located in the granule cell layer and sub-granular zone of the dentate gyrus and are noted to exhibit morphological characteristics of granule neurons via expression of an immature granule neuron marker (TOAD-64), p. 5797, column 1. As the neurons are noted to be immature, capable of subsequent differentiation and proliferation the neuronal type cells are deemed to be neural stem cells consistent with Applicants specification and discussion of neural stem cells having such properties, see specification pp. 7-8. Moreover, the estrogen is provided to animals in vivo. As the rats inherently comprise neural stem cells located in the brain, and subventricular zone (claims 2-3), the in vivo provision of estrogen produced within the female animals or injection of estradiol provide for the limitations of claims 1-3. Here it is particularly noted that it is not the increased numbers of neural stem cells that are limited to locale, but merely the provision of an effective amount to at least one neural stem cell. As the provision of estrogen or estradiol is provided to the animals compising neural stem cells and the circulatory system would distribute the hormone or drug throughout the body tissues, the in vivo production or administration via injection would achieve administration to the brain, subventricular zone, ventricle and systemically as in claims 2-5. The rats are noted to be mature adults, p. 5793, column 1, first paragraph. Hence, the reference teachings anticipate the claimed invention, in particular as directed to providing an effective amount of an estrogen to at least one neural stem cell

under conditions which result in an increase in the number of neural stem cells.

11. Claims 1-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al., Hormones and Behavior, 39:11-21, 2001 (5-20-02 IDS reference).

Smith et al., teach that estrogen provided by stimulation of behavioral estrus in female prarie voles provides for increased numbers of BrdU-labeled neurons in the rostral migratory stream via the subventricular zone of the brain, see in particular Title, Abstract. The subventricular is a recognized source of neural stem cells within the adult mammalian brain, see also p.11-12. Moreover, the estrogen is provided to animals in vivo as stimulated via exposure to males or via injection administration of estradiol benzoate. As the rats inherently comprise neural stem cells located in the brain, and subventricular zone (claims 2-3), the in vivo provision of estrogen produced within the female animals or injection of estradiol provide for the limitations of claims 1-3. Here it is particularly noted that it is not the increased numbers of neural stem cells that are limited to locale, but merely the provision of an effective amount to at least one neural stem cell. As the provision of estrogen or estradiol is provided to the animals compising neural stem cells and the circulatory system would distribute the hormone or drug throughout the body tissues, the in vivo production or administration via injection would achieve administration to the brain, subventricular zone, ventricle and systemically as in claims 2-5. The rats are noted to be mature adults, pp. 12-13. Hence, the reference teachings anticipate the claimed invention, in particular as directed to providing an effective amount of an estrogen to at least one neural

stem cell under conditions which result in an increase in the number of neural

stem cells.

Status of Claims

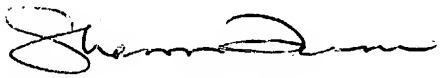
12. No claims are allowed.

13. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.



Sharon L. Turner, Ph.D.
July 22, 2004

SHARON L. TURNER, PH.D.
PATENT EXAMINER